REMARKS

Claims 26, 27 and 29-36 are currently pending and under consideration in the above-identified application.

REJECTION UNDER 35 U.S.C. § 103(a)

Claims 26, 27 and 29-36 remain rejected under 35 U.S.C. § 103(a), allegedly, as obvious over U.S. Patent No. 5,686,432 to Baggio et al. ("Baggio") in combination with U.S. Patent No. 5,252,339 to Cristofori et al. ("Cristofori") and U.S. Patent No. 5,496,807 to Marchi ("Marchi") for reasons of record. Applicants respectfully disagree with the rejection.

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). The suggestion of the claimed invention must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir 1988). Moreover, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). This showing of combinability must be "clear and particular". *In re Dembiczak*, 175 F.3d 994, 999; 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999).

Cristofori teaches a pharmaceutical composition for oral administration of 25 to 500 mg of glycosaminoglycans, including but not limited to sulodexide, in the form of a gastro-resistant coated formulation. However, Cristofori does not teach or suggest the administration of sulodexide for the treatment of diabetic nephropathy. Cristofori teaches that the administration of sulodexide is for the "prevention and treatment of thrombotic and atherosclerotic pathologies" (column 2, lines 50-51) and that administration of sulodexide is in such manner for "best performance of the anticoagulant, fibrinolitic antithrombotic, antitherosclerotic and antihyperlipoproteineic activities" (column 2, lines 55-58). This publication is completely silent as regards diabetic nephropathy.

Marchi teaches dosages of 500 to 1500 LRU sulodexide per day to treat diabetic nephropathy, which is equivalent to 50 to 150 mg per day. Marchi does not teach a method for treating diabetic nephropathy by administering more than 150 mg sulodexide per day. In fact, Marchi administered only either (a) two capsules containing 250 LRU (25 mg) twice a day (column 3, lines 10-16 and column 4, lines 24-26 of Marchi); or (b) an injection of 600 LRU (60 mg) once a day (column 3, lines 35-40). This publication only provides evidence from clinical trials where the amounts of sulodexide administered are approximately one-fourth of the minimal amount taught and claimed in the present application.

With regard to the teachings of Baggio, the passage quoted by the Examiner is found in the background section of Baggio and merely characterizes the results described in Marchi (discussed above) using a low dose of sulodexide. The citation referred to by Baggio, EP 0624374, is the European counterpart of Marchi. Since the Examiner is only using Baggio by quoting a characterization of the results of March, Applicants believe that Baggio is redundant in the rejection. Applicants note that Baggio, like Marchi does not teach or suggest oral administration of high dosages of sulodexide.

Baggio actually teaches administering sulodexide to improve the performance of CAPD (Continuous Ambulatory Peritoneal Dialysis) by lowering the protein loss in the

dialytic liquid thereby preventing structural and functional alterations of the peritoneal membrane by improving the capability and the selectivity of the filtration of the peritoneal membrane (*e.g.*, column 1, lines 14-15, column 2, lines 60-64). Thus, the method taught by Baggio is to treat patients undergoing ambulatory dialysis by administering directly to the peritoneum a dialysis liquid containing sulodexide. Baggio teaches that sulodexide is intended to prevent or slow the deterioration of the peritoneal membrane by local administration to the peritoneal cavity. Sulodexide is not intended to work in the kidney and, in fact, cannot do so since the mode of administration taught by Baggio does not place sulodexide in the circulatory system so that sulodexide can reach the kidney.

Furthermore, although Baggio discloses administering a maximum of 500 mg of sulodexide intraperitoneally, a reading of the actual clinical trial set forth in Example 4 shows that the actual dosage used was only 50 mg of sulodexide administered in a single nocturnal exchange of the fluid (column 5, lines 64-66), which amount of sulodexide was further diluted by the additional four washes with dialysis liquid without sulodexide.

The Examiner's rejection appears to allege that combining Baggio (teaching of administrations of high dosages of sulodexide to the peritoneal cavity, NOT oral administration) with Cristofori (teaching of oral administration) and Marchi (teaching of treatment of diabetic nephropathy by oral administration of low dosages of sulodexide) would have allowed one of skill to arrive at the presently claimed invention. However, the Examiner mistakenly extrapolates dosages for oral (systemic) administration from dosages used in peritoneal delivery. The Examiner fails to take into account the well known anti-thrombosis activity of sulodexide, which is a concern where sulodexide is administered systemically, *i.e.*, enters the blood stream. Such a concern is not relevant with peritoneal administration of sulodexide, since peritoneal administration does not permit sulodexide to enter the blood stream. Moreover, Applicants note that Baggio did not administer more than 50 mg/day sulodexide. It would appear that such dosage was further diluted by the additional

four washes without sulodexide.

Thus, Applicants respectfully submit that those of skill in the art would not have extrapolated the teachings of Baggio to oral administration since the distribution of sulodexide in the body administered to the peritoneum is substantially different from the distribution of sulodexide administered orally. Thus, one skilled in the art would not take Baggio as a teaching that high dosages of sulodexide can be administered orally. Further, the teachings of Cristofori (oral administration) and/or Marchi (treatment with low doses) do not fill in the gap.

The Federal Circuit has stated that in determining whether a claim is obvious requires the oft-difficult but critical step of casting the mind back to the time the invention was filed to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. Close adherence to this methodology is especially important in the case of less technologically complex inventions, where the very ease with which the invention can be understood may prompt one to fall victim to the insidious effect of hindsight reconstruction wherein that which on the inventor taught is used against its teacher. *In re Dembiczak*, 175 F.3d 994, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). Such hindsight reconstruction does not meet the legal standard for obviousness. It is error to reconstruct the claimed invention from the prior art by using the claims as a blueprint. "When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir 1985). Otherwise, simply combining prior art references without evidence of the required suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability, which is the essence of hindsight. *In re Dembiczak*, 175 F.3d 994, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999).

The Federal Circuit has stated that the best defense against a hindsight-based

obviousness analysis is rigorous application for the requirement for a showing of the teaching or motivation to combine the prior art references. *In re Dembiczak*, 175 F.3d 994, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). In the instant application, Applicants submit that the Examiner has not provided the required suggestion, teaching or motivation to combine the teachings of Baggio and/or Marchi (treatment with low doses) and Cristofori (oral administration) to render a claim directed to treating a patient with diabetic nephropathy with a high dosage of sulodexide. Applicants respectfully submit that none of the cited references provide the required suggestion or expectation to render obvious the claimed invention.

Moreover, Applicants submit, as taught in the specification on page 8, lines 7-35, that daily oral administration of 200 mg sulodexide improved the therapeutic effects of sulodexide (75% reduction of AER as compared to 50% reduction using 100 mg sulodexide during the experiment period) and maintained the beneficial effects for a longer period of time (maintenance of 65% reduction of AER with the 200 mg daily dosage, as compared to maintenance of 28% with the 100 mg daily dosage as measured at 4 months after termination of the trial). Thus, a higher dosage of sulodexide have a significantly better therapeutic index and a significantly longer period of therapeutic effect, without adverse side effects, as compared to a dosage of 100 mg per day. Thus, the use of a high dosage of sulodexide provides unexpected results. Applicants note that the Examiner has requested secondary proof but has not taken into account these experimental results or provided a reasoned explanation as to why they are irrelevant in his analysis.

Therefore, in view of the foregoing, Applicants respectfully submit that the Section 103 rejection has been overcome, and thus, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the remarks of the present response be entered and made of record in the present application. Claims 26, 27 and 29-36 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejection and allowance and action for issuance are respectfully requested.

Applicants request that the Examiner call Geraldine F. Baldwin at (212) 790-2296 if any questions or issues remain.

Respectfully submitted,

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Geraldine F. Baldwin 31,232
Geraldine F. Baldwin (Reg. No.)

By: William Thomann 40,203
William Thomann (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 790-2803

Enclosures